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09/557,001	04/20/2000	Byoung Joo Gwag	0217-0001	6241

7590 01/29/2002  
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EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 01/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/557,001

Applicant(s)

GWAG ET AL.

Examiner

Paul A. Zucker

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8 and 9 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8 and 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7. 6) ☐ Other:

**DETAILED ACTION**

***Final Rejection***

***Current Status***

1. This action is responsive to Applicant's amendment of 20 December 2001 in Paper No 6 responsive to the Office Action of 23 July 2001 in Paper No 5.
2. Receipt and entry of Applicant's amendment is acknowledged. The objections set forth in ¶ 1 of the previous Action are withdrawn.
3. Receipt and entry of the substitute specification is acknowledged.
4. Applicant's cancellation of 7 is hereby acknowledged. Claims 1-6 and 8-9 remain outstanding.
5. The rejection of Claim 9 under 35 USC §112 set forth in ¶ 2 of the previous Office Action is withdrawn in view of Applicant's amendment of the claim.
6. The rejections of Claims 1-9 under 35 USC §103 set forth in ¶ 4 of the previous Action are withdrawn as moot in view of Applicant's amendment of the claims.
7. The rejections of Claims 1-3, 5 and 7-9 under 35 USC §102 set forth in ¶ 3 of the previous Office Action are withdrawn in response to Applicant's arguments and amendments.
8. Claim 4 is finally rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al (US 3,674,844 07-1972) for the reasons of record as set forth in ¶ 3 of the previous Office Action.
9. Claims 1-6 and 8-9 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Spector et al (The Journal of Pharmacology and Experimental

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Therapeutics, 1974 188(2) pages 55-65) and further in view of Kumamoto et al (Japanese Journal of Pharmacology 1997, 75, pages 187-189) and further in view of Shen et al (US 3,674,844 07-1972) as set forth below.

10. Claims 1-3 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Shen et al (US 3,674,844 07-1972) as set forth below.

### ***Information Disclosure Statement***

11. The information disclosure statement filed 20 December 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The first and fourth non-patent documents (Myrsk et al and Rizzi et al) were not provided and thus could not be considered.

### ***Response to Arguments***

12. In view of the withdrawal of all rejections except Claim 4 under 35 USC §102 Applicant's arguments have been rendered moot with regard to the rejection under 102.
13. Applicant's amendment of Claim 4 fails to obviate the rejection under 35 USC §102 set forth in ¶ 3 of the previous Office Action. Compounds such as 5-(p-fluorobenzylamino) salicylic acid are explicitly exemplified (Example 3, Column 5, lines 50-68).

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14. Applicant's arguments filed 23 October 2001 with regard to the rejections under 35 USC §103 have been fully considered but they are not persuasive. The Examiner's response to Applicant's arguments are set forth below.
15. With regard to the arguments to the rejections under 35 USC §103 the Applicant argues that the compounds of the invention show a triple neuroprotective action that cannot be obtained only through by the aminosalicylate moiety and that substitution of the amino group by a phenyl, or substituted phenyl group, leads to an unexpected improvement of the antioxidant power of the aminosalicylate moiety. Applicant appears however to rely heavily on the well-known effects of aminosalicylates as protectants against oxidative stress which is well understood in the art. The utility of aminosalicylates as inhibitors of the damaging effects of oxidative stress is well established in the art as shown by Kumamoto's teaching that aminosalicylates inhibit lipid peroxidation in rat intestinal mucosa after ischemia, resulting from hypoxia, possibly by scavenging the oxygen derived free radicals (Page 187, left column, lines 2-8). The Examiner would like to reiterate that Shen teaches the substitution of the aminosalicylate group and administration of the substituted aminosalicylates. While applicant points out the additional advantages of Shen's (and closely related) compounds, the discovery of a previously unrecognized mechanism of action does not impart patentability to a method which is old in the art. Shen's disclosure (Column 3, lines 1-3) of superior potency and decreased side effects is sufficient motivation to employ the substituted aminosalicylates. Applicant's comment (page 7, lines 20-23) with regard to aspirin showing the same effect as far as  $Zn^{2+}$  toxicity

underscores the point that the effect, though it may vary depending upon substitution, is present in the aminosalicylate of Spector who teaches the neuro-availability of aminosalicylates.

16. With regard to the arguments to the rejections under 35 USC §103 Applicant further argues that one of ordinary skill in the art would not inherently recognize that the compounds of Shen show the additional activities demonstrated by Applicant. Such recognition is, however, unnecessary since one of ordinary skill in the art would be motivated by the known antioxidant properties of the compounds to employ them for the instant intended purpose.

### ***New Rejections***

The following new rejections and objections are necessitated by Applicant's amendment of the claims. These rejections and objections are accordingly MADE FINAL.

### ***Claim Rejections - 35 USC § 112***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

17. Claims 1-3 and 5 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3 and 5 recite the limitations "(wherein, n is an integer of 1 to 5, inclusive)" and /or "(wherein, n is an integer of 1

to 5, inclusive)". The use of parentheses renders the claim indefinite because it is unclear whether the limitation(s) enclosed within are part of the claimed invention.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

18. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shen et al (US 3,674,844 07-1972). Shen discloses (Column 1, line 28-Column 2, line 71) a genus of 5-amino-salicylic acid derivatives which render obvious the instant claimed genus. Compounds such as 5-(p-fluorobenzylamino) salicylic acid are explicitly exemplified (Example 3, Column 5, lines 50-68). The corresponding para-trifluoromethyl, and para-chloro compounds are disclosed by reference to the general procedure (Example 2, Column 5, lines 29-41). The corresponding benzoyl compounds such as 5-(4-nitrobenzoyl) amino salicylic acid are disclosed as well (Example 1, Column 4, line 60-Column 5, line 16, especially Column 4, line 73). The compounds of instant Claims 1-3 where  $n = 2$ , are obvious over those of Shen since they are simply adjacent homologues (and thus *prima facie* obvious over Shen) having a single additional methylene group inserted between the amino group and the phenyl ring. Similarly, the compounds where  $R_3$  is acetoxy are *prima facie* obvious over those of Shen because they correspond to simple N-protected versions of the compounds of Shen. The acetoxy- group is well known readily removable protecting group.

19. Claims 1-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Spector et al (The Journal of Pharmacology and Experimental Therapeutics, 1974 188(2) pages 55-65) and further in view of Kumamoto et al (Japanese Journal of Pharmacology 1997, 75, pages 187-189) and further in view of Shen et al (US 3,674,844 07-1972). Spector discloses a study of the concentration of para-aminosalicylic acid (PAS) in cerebrospinal fluid. This disclosure teaches that PAS crosses the blood-brain barrier and thus can be expected to reach therapeutically effective concentrations at the target site (page 55-56, whole first paragraph).

Kumamoto teaches that aminosalicylates inhibit lipid peroxidation in rat intestinal mucosa after ischemia, resulting from hypoxia, possibly by scavenging the oxygen derived free radicals (Page 187, left column, lines 2-8). PAS (5-ASA according to Kumamoto) inhibited peroxide formation in a dose dependant manner (page 189, left column, line 1). Shen teaches (Column 1, line 28-Column 2, line 71) a genus of 5-amino-salicylic acid derivatives for administration as therapetic compounds(Column 2, line 72-Column 3, line 3) over which the instant compounds are prima facie obvious as either adjacent homologues or simple protected analogs. Thus it would have been obvious for one of ordinary skill in the art to have realized that oxidative stress and associated cerebral disease could be treated with the PAS derivatives taught by Shen. The motivation is to provide an improved method of delivering PAS and its derivatives to the target organ. The expectation for success would be high since the administration of these compounds is known.



20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

21. Claims 1-6 and 8-9. Claims 1-6 and 8-9 are finally rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Geist can be reached on 703-308-1701. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

PAZ

January 28, 2002

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

PAZ  
January 22, 2002



**GARY GEIST**  
**SUPERVISORY PATENT EXAMINER**  
**TECH CENTER 1600**